Inhaled nitric oxide in patients with normal and increased pulmonary vascular resistance after cardiac surgery


SUMMARY
We studied the haemodynamic effects of inhaled nitric oxide 40 p.p.m. in two groups of patients after cardiac surgery (mitral valve surgery or coronary artery bypass grafting). Nitric oxide caused a significant reduction in pulmonary vascular resistance after mitral valve surgery in patients who had pre-existing pulmonary hypertension, but no change in haemodynamic state in the coronary artery bypass group of patients, who had normal pulmonary arterial pressures. (Br. J. Anaesth. 1994; 72: 185-189)

KEY WORDS

Nitric oxide is being recognized increasingly as one of the key mediators in the balance of factors regulating vascular tone [1-4]. It is the active moiety of endothelium derived relaxation factor [5], and has been shown to exert potent vasodilator effects by stimulation of smooth muscle guanylate cyclase in isolated vascular preparations and in animal and clinical studies [6-8]. Nitric oxide is deactivated by reaction with haemoglobin and reactive oxygen species; these processes are rapid and result in the evanescent and localized effects of nitric oxide [9,10]. Administration of exogenous nitric oxide by inhalation may thus be predicted to produce dilatation of the pulmonary vascular bed in proximity to the broncho-alveolar system without producing systemic haemodynamic effects [11,12]. Addition of nitric oxide to inhaled gases has been shown to reduce selectively pulmonary vascular resistance (PVR) and mean pulmonary artery pressure (MPAP) in patients with ARDS [13], persistent fetal circulation [14] and secondary pulmonary hypertension [15,16], and to counteract hypoxic pulmonary vasoconstriction in volunteers breathing hypoxic gas mixtures [17]. Several groups of cardiac surgical patients may benefit from therapeutic use of nitric oxide for selective manipulation of the pulmonary circulation; these include heart transplant recipients [18], patients with pulmonary hypertension [16] and patients with end-stage cardiac failure awaiting transplantation. Pulmonary hypertension, defined as MPAP exceeding 22 mm Hg or systolic PAP greater than 30 mm Hg [19], is a common feature in patients with chronic mitral stenosis. After mitral valve surgery, pulmonary venous congestion subsides, but the endothelial and smooth muscle changes accompanying chronic pulmonary hypertension take longer to resolve. PAP and PVR may thus remain increased for some time after operation and may occasionally lead to clinically significant impairment of cardiac function. Therefore, we studied the effects of inhaled nitric oxide on pulmonary and systemic haemodynamic variables, with specific measurement of indices of right ventricular function in the immediate postoperative period after mitral valve surgery and coronary artery bypass grafting.

PATIENTS AND METHODS
After obtaining Ethics Committee approval and written informed consent, we studied 12 patients undergoing elective mitral valve repair or replacement (MVR) and 10 patients undergoing elective coronary artery bypass grafting (CABG). All patients had good left ventricular function as determined by angiography or echocardiography and no other significant organ dysfunction. The MVR patients had long histories of mitral valve dysfunction with mean pulmonary artery pressures greater than 20 mm Hg (measured during assessment for surgery) and no evidence of ischaemic heart disease.

The study was conducted during the first 2 h after operation. Sedation was maintained during this period with propofol 1.5-3.0 mg kg⁻¹ hr⁻¹ (no significant difference in total dose of propofol between the two groups). The patient’s trachea was intubated and the lungs ventilated mechanically with an air-oxygen mixture (FiO₂ 0.5-0.6) to normocapnia. After a short period (less than 30 min) of stabilization in the intensive care unit, nitric oxide was administered in a concentration of 40 p.p.m. via the ventilator, for a period of 20 min. Patients were defined as being stable when heart rate, arterial pressure and pulmonary capillary wedge pressure did not fluctuate by more than 5 % over a period of 5 min. The study was completed 10 min after cessation of nitric oxide.


Correspondence to R.D.L.
Central venous pressure (CVP), diastolic and systolic pulmonary artery pressures (DPAP, SPAP) and diastolic and systolic arterial pressures (SAP, DAP) were monitored invasively and displayed continuously along with mean pulmonary and systemic arterial pressures (MPAP, MAP). Cardiac output, right ventricular volume and pulmonary capillary wedge pressure (PCWP) were measured by thermodilution using a 7.5-French gauge right ventricular ejection fraction catheter (Baxter, Irvine, CA). A Baxter cardiac output and ejection fraction computer (Model REF-1-220/240) was used to compute values for cardiac index (CI), right ventricular end-diastolic and end-systolic volume index (EDVI, ESVI) and right ventricular ejection fraction (RVEF). Pulmonary and systemic vascular resistance (PVR and SVR) were calculated using standard formulae.

Thermodilution and pressure measurements were recorded at four times during the study: baseline (T1), after 10 min of ventilation with nitric oxide 40 p.p.m. added to the inspired gas (T2), after 20 min of ventilation with nitric oxide 40 p.p.m. (T3) and 10 min after cessation of nitric oxide (T4). Blood samples were obtained at each of these times for measurement of arterial and mixed venous blood-gas tensions and co-oximetry.

The nitric oxide delivery system utilized two systems in parallel, one containing air-oxygen and the other nitric oxide-nitrogen with mixing occurring just before reaching the patient. This minimized effectively the time nitric oxide and oxygen were in contact and thus the conversion of nitric oxide to the more toxic nitrogen dioxide. Concentrations of inhaled nitric oxide and nitrogen dioxide were measured with a chemiluminescence analyser (Model 42 Thermo Environmental Instruments Inc., U.S.A.) and co-oximetry was used to measure methaemoglobin concentrations.

Statistical analysis

Haemodynamic data were expressed as median and range and compared with the baseline values at T1 using the Wilcoxon test with Bonferroni’s correction. P < 0.05 was taken as statistically significant.

RESULTS

On completion of surgery, five patients were excluded from the study because of arrhythmias (two), requirement for inotropic support (two) and the use of intra-aortic balloon counterpulsation (one). Nine MVR and eight CABG patients were considered suitable to be studied on completion of surgery. The only nitrate used in each group after operation was sodium nitroprusside (SNP), for control of arterial pressure (three patients in the CABG group and two patients in the mitral group). However, this was not infused during the study, except in two patients in the CABG group.

Changes in haemodynamic variables (median (range) values for the groups) are shown in table 1; changes in individual patients in the two groups are shown in figures 1 (pulmonary vascular resistance) and 2 (systemic vascular resistance).

| Table 1. Haemodynamic variables in patients after mitral valve surgery or coronary artery bypass grafting, who received nitric oxide 40 p.p.m. (median (range)) |
|---|---|
| | Mitral valve surgery |
| | CABG group |
| | MVR group |
| | T1 | T2 | T3 | T4 |
| | T1 | T2 | T3 | T4 |
| | | | | |
| CI (l/min/m²) | 8.0 (7.2-11.8) | 8.0 (7.2-10.2) | 8.0 (7.2-10.2) | 8.0 (7.2-10.2) |
| MPAP (mm Hg) | 18 (9-25) | 18 (9-25) | 18 (9-25) | 18 (9-25) |
| MAP (mm Hg) | 90 (75-105) | 90 (75-105) | 90 (75-105) | 90 (75-105) |
| DPAP (mm Hg) | 19 (9-25) | 19 (9-25) | 19 (9-25) | 19 (9-25) |
| SPAP (mm Hg) | 21 (15-25) | 21 (15-25) | 21 (15-25) | 21 (15-25) |
| SAP (mm Hg) | 112 (94-132) | 112 (94-132) | 112 (94-132) | 112 (94-132) |
| PVR (dyns c-sec/m²) | 1,544 (1,372-2,560) | 1,544 (1,372-2,560) | 1,544 (1,372-2,560) | 1,544 (1,372-2,560) |
| SVR (dyns c-sec/m²) | 2,448 (2,136-2,905) | 2,448 (2,136-2,905) | 2,448 (2,136-2,905) | 2,448 (2,136-2,905) |
| PCWP (mm Hg) | 7 (5-9) | 7 (5-9) | 7 (5-9) | 7 (5-9) |
| EDVI (ml/m²) | 32 (24-40) | 32 (24-40) | 32 (24-40) | 32 (24-40) |
| ESVI (ml/m²) | 20 (12-24) | 20 (12-24) | 20 (12-24) | 20 (12-24) |
| RVEF (%) | 48 (31-63) | 48 (31-63) | 48 (31-63) | 48 (31-63) |

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INHALED NITRIC OXIDE

FIG. 1. Effects of nitric oxide on pulmonary vascular resistance (PVR) in individual patients after mitral valve surgery (left) or coronary artery bypass grafting (right). T1 = Baseline; T2 = after 10 min nitric oxide; T3 = after 20 min nitric oxide; T4 = 10 min after cessation of nitric oxide.

FIG. 2. Effects of nitric oxide on systemic vascular resistance in individual patients after mitral valve surgery (left) or coronary artery bypass grafting (right). T1 = Baseline; T2 = after 10 min nitric oxide; T3 = after 20 min nitric oxide; T4 = 10 min after cessation of nitric oxide.

After inhalation of nitric oxide, the MVR group demonstrated a statistically significant reduction in PVR of about 20–30% (P < 0.05), and an insignificant decrease in SVR. The reduction in PVR was associated with a significant decrease in DPAP and MPAP (P < 0.05). The CABG group showed no significant change in any haemodynamic variable after inhalation of nitric oxide.

DISCUSSION

The accepted criterion for determining if an agent has induced significant pulmonary vasodilatation is a decrease in PVR of 20–30% [20–22]. The work of the right ventricle may be taken into account by including the additional criterion of a 10% decrease in MPAP [23]. In our study, nitric oxide fulfilled these criteria for an active pulmonary vasodilator in patients with pulmonary hypertension after mitral valve surgery. Furthermore, as no significant changes in systemic pressures or resistance were observed, nitric oxide was selective in its effects.

With filling pressures held constant, PVR and MPAP were reduced, but RVEF remained unchanged. The decrease in MPAP resulted from a reduction in DPAP. Systolic PAP and RVEF are related inversely [24–27] and the lack of change in RVEF in this study is consistent with our finding that SPAP was not affected by inhaled nitric oxide. A previous study [15] using inhaled nitric oxide after mitral valve replacement found that the nitric oxide-induced changes in MPAP resulted from a proportional decrease in both DPAP and SPAP. The patients in our study had markedly smaller values of pulmonary pressure and resistance than those reported in the earlier study [15], which may account for the apparent discrepancy.

In an early article on the pathophysiology of mitral stenosis, Wood [28] regarded the ensuing pulmonary hypertension as progressive, incorporating stages of
congestion, hypertrophy and spasm. Experimental models for pulmonary hypertension [29-31] support the concept of sequential changes, with arterial vessels less than 500 μm in diameter affected primarily. Animal models for hypertension [32,33] highlight the weakened endothelium-dependent relaxation, with an overall decrease in the release of EDRF/prostacyclin, decreased smooth muscle cell responsiveness and increased release of vasoactive constriction factors. We hypothesize that the reduction in MPAP, ascribed chiefly to a decrease in DPAP, was the result of nitric oxide recruitment of pulmonary vessels with dysfunctional endothelium. This is borne out by our finding that inhaled nitric oxide had no haemodynamic effects in patients with normal pulmonary pressures and resistance after CABG. Presumably, pulmonary endothelial function was unimpaired in these patients and basal endogenous nitric oxide production was maintained such that exogenous nitric oxide had little further effect.

In keeping with similar studies [14-16], we used a concentration of nitric oxide 40 p.p.m. It has been suggested [13] that a concentration of nitric oxide less than 20 p.p.m. may be just as efficacious. This smaller concentration may limit toxicity and there is scope for more studies to determine the minimum therapeutic concentration.

In conclusion, we have shown that inhaled nitric oxide in a concentration of 40 p.p.m. acted as a selective pulmonary vasodilator in patients with pre-existing pulmonary hypertension, but not in those with normal pulmonary arterial pressures.

REFERENCES

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